REMARKS

Claims 1-17 are pending in the instant application. Claims 1-17 have been rejected. Claims 1 and 11 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Defective Oath or Declaration

The Examiner suggests that the oath or declaration is defective because a non-initialed and/or non-dated alteration was made to the original Declaration. Accordingly, in an earnest effort to advance the prosecution of this case, Applicants are providing herewith a new Declaration.

II. Rejection of Claim 11 under 35 U.S.C. § 112, second paragraph

Claim 11 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention. Specifically, the Examiner suggests that there is insufficient antecedent basis for the limitation "said PDB". Accordingly, in an earnest effort to advance the prosecution of this case, Applicant has amended claim 11. The term "PDB" has been deleted and replaced with --protein data bank--, a term for

which there is antecedent basis in the claim. Withdrawal of this rejection is respectfully requested.

III. Rejection of Claims 1, 11 and 13 under 35 U.S.C. § 102(b)

Claims 1, 11 and 13 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Wallace et al. (Protein Science (June 1996) 5:1001-1013). Applicants respectfully traverse this rejection.

In accordance with MPEP § 2131 to anticipate a claim, the reference must teach every element of the claim. Wallace et al. does not teach every element of the claimed method. In particular, Wallace et al. does not teach identification of putative polypeptide domains as set forth in step (A) nor determination of a three dimensional structure of the polypeptide domain as set forth in step (B) of claim 1. As discussed at page 11 of the instant application, a protein domain identified in accordance with step (A) of claim 1 generally involves 50 to 300 amino acids. In contrast, in the method of Wallace et al. a triad of 3 amino acids is identified. Further, the 3D templates taught at page 1004-1005 of Wallace et al. and suggested by the Examiner to be analogous to step (B) of claim 1, were derived from **known** three dimensional protein structures. From the known three-dimensional structure of a protein already taught in a database, Wallace et al. then

determine its biochemical function. Nowhere, however, do Wallace et al. teach a method for determining biochemical function of a protein or polypeptide domain of **unknown** three dimensional structure.

As taught throughout the specification, the instant invention relates to high throughput methods and systems based upon automated technologies which use linear sequence information on a genomic scale to determine previously unknown three-dimensional structures of proteins as well as their biological functions. In an earnest effort to highlight distinguishing elements of the present invention from methods taught in prior art references such as Wallace et al., Applicants have amended claim 1 to state in the preamble that the method is used for determining biochemical function of a protein or polypeptide domain of **unknown** three dimensional structure. Support for this amendment can be found throughout the specification wherein it is reiterated that the present invention describes a system or method for rapid determination of the three dimensional structures of proteins and protein domains. Additional support for this amendment is found in step (B) of claim 1 which states that the three dimensional structure of the stable polypeptide domain is determined.

Since Wallace et al. does not teach a method wherein polypeptide domains are identified and the unknown three dimensional structure of the protein or polypeptide domain is determined, this reference can not anticipate claim 1 as amended or claims 11 or 13 which depend therefrom. Withdrawal of this rejection is therefore respectfully requested.

IV. Rejection of Claims 1, 5-9, 11 and 13 under 35 U.S.C. § 103(a)

Claims 1, 5-9, 11 and 13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. in view of Friedrichs et al. (J. Biomol. NMR (1994) 4:703-726). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time this invention was made to combine the 3-D structural alignment and function determination method of Wallace et al. with use of NMR structure determination of Friedrichs since Wallace et al. state "This suggests that the development of databases of 3D templates, such as those that currently exist for protein sequence templates, will help identify the functions of new protein structures as they are determined and pinpoint their functionally important regions.

Claims 1-9, 11, 13 and 14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al. in view of Friedrichs et al. and further in view of Farber et al. (J. Mol.

Biol. (1992) 226:471-479). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Wallace et al. in view of Friedrichs et al. with the database preparation method of Farber et al. since Farber et al. notes "Simple neural networks predict coding regions in DNA very well when trained on representation of DNA using single codon frequencies (Page 478, column 1)." The Examiner suggests that an ordinary practitioner would have been motivated to combine the method of Wallace et al. in view of Friedrichs et al. with the protein coding determinations of Farber et al. in order to maximize the usable databases to identify homologous proteins and thereby determine the function of unknown proteins.

Claims 1, 5-11 and 13 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. in view of Friedrichs et al. and further in view of Bagby et al. (J. Biomol. NMR (1997) 10:279-282). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the button test of Bagby et al. with the NMR and functional determination method of Wallace et al. in view of Friedrichs et al. since Bagby et al. state "The button test is an efficient, small scale way of tackling this

problem (page 281, column 1)." The Examiner suggests that the ordinary practitioner would have been motivated to utilize the button test to optimize solubility for NMR since it is expressly noted as efficient and small scale, which reduces time and wasted reagents, which for purified proteins can represent a large investment of time and money.

Claims 1-9 and 11-17 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. in view of Friedrichs et al. and further in view of Farber et al. (J. Mol. Biol. (1992) 226:471-479) and further in view of Orengo et al. (Structure (August 1997) 5:1093-1108). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the CATH method of Orengo et al. with the NMR and functional determination method of Wallace et al. in view of Friedrichs et al. and further in view of Farber et al. since Orengo et al. state "A database of well-characterized protein structure families, such as CATH, will facilitate the assignment of structure-function evolution relationships to both known and newly determined proteins structure (abstract)." The Examiner suggests that the ordinary practitioner would have been motivated to combine the reagents, software and apparatus used in the methods of Wallace et al. in view of

Friedrichs et al. and further in view of Farber et al. and further in view of Orengo et al. into an integrated system for determination of protein function from protein structure in order to simplify the determination of protein function by collecting reagents of use in an obvious method into a single location to improve ease of use and minimize effort.

Applicants respectfully traverse these rejections.

MPEP § 2143 states that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references when combined must teach or suggest all the claim limitations.

As discussed in Section III, *supra*, the primary reference by Wallace et al. does not teach two essential steps in the method of claim 1, namely the identification of protein domains and the determination of three-dimensional structure. Nor is there any suggestion of these steps as Wallace et al. teaches use of a triad of amino acids and a protein structure database to identify function of proteins with a known structure. Thus, the primary

reference also fails to provide any teaching or suggestion of the system of claim 15 which comprises a first computer algorithm capable of parsing a target polynucleotide into at least one putative domain encoding region (element A of claim 15) or a third computer algorithm capable of determining tertiary structure of a polypeptide (element (G) of claim 15) or the method of claim 17 wherein the putative polypeptide domain is identified in step (A) and the three dimensional structure of the polypeptide domain is determined in step (D).

Secondary references cited in these obviousness rejections fail to remedy the deficiencies in the primary reference.

The teachings of Friedrichs et al. are related to an automated system for protein ^{15}N, ^{13}C, and ^{1}H NMR resonance assignments from a set of three-dimensional NMR spectra. While resonance assignments are useful in establishing the three dimensional structure of protein, this information alone is insufficient for three dimensional structure determination. Accordingly, this reference also provides no teaching or suggestion with respect to either identification of protein or polypeptide domains or the determination of unknown three-dimensional protein structures as claimed in the instant invention.

Farber et al. disclose a neural network and information theory for determination of coding regions for eukaryotic proteins in raw sequence base information. Thus, this reference also provides no teaching or suggestion with respect to identification of protein or polypeptide domains and determination of three-dimensional proteins structures.

Similarly references by Bagby et al. and Orengo et al. fail to teach or suggest these claim limitations. As acknowledged by the Examiner, the teachings of Bagby et al. are related to preparation of samples for NMR analysis while the teachings of Orengo et al. are limited to the use of the CATH method for classification of protein domains, the three dimensional structures of which are known.

As set forth by both the Court of Appeals for the Federal Circuit and the MPEP, when an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and MPEP § 2143.03. Thus, while some of the secondary references may teach or suggest specific elements as set forth in the dependent claims, the cited combination of references fail to teach or suggest all the limitations of the method or system as set forth in independent claims 1, 15 and 17. Accordingly, the cited combinations of prior

art references can not render obvious the instant claimed invention. Withdrawal of these rejections is therefore respectfully requested.

V. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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